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Review

The Developmental Origins of Obesity and Related Health Disorders – Prenatal and Perinatal Factors

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A B S T R A C T

Obesity, and its health-related sequelae (the metabolic syndrome), have recently emerged as a global health crisis. The prevalence of childhood and adult obesity in economically developed and developing countries world-wide has more than doubled over the past decade. While genetic factors, increasingly sedentary lifestyles, and overnutrition have all been cited as important components of the obesity crisis, recent epidemiological and experimental evidence suggests that developmental factors – especially those that occur in utero and during early postnatal life – play a significant role in the pandemic. Research into the 'developmental origins of health and disease' (DOHaD) has now firmly established that pre- and perinatal developmental perturbations which predispose to obesity in adult life can result from a variety of factors, including both nutritional surplus and deficiency, and there is growing evidence that these physiological traits can be passed on epigenetically to subsequent generations. Anthropological perspectives regarding the developmental origins of obesity and its related health problems cannot only shed further light on contemporary ethnic human health disparities, but can offer unique insights into the relevance of the developmental origins of disease to community-based public health interventions.

Key words: *obesity, pandemic, DOHaD, prenatal, perinatal, anthropology*

Introduction

According to a 2005 World Health Organization (WHO) report, at least 400 million adults world-wide meet the most commonly used weight-for-height criterion for obesity: a body mass index (BMI) of 30 or greater. An additional 1.6 billion adults globally are classified as »overweight« using the standard BMI cutoff of 25 or greater[1]. Addressed as a major threat to global health by WHO only in the last decade, obesity, defined as »the accumulation of adipose tissue to excess and to an extent that impairs both physical and psychosocial health and well-being«[2], has rapidly emerged as a world-wide pandemic.

Although some studies have called into question the effect obesity per se has on excess mortality[3], the health risks of obesity-related sequelae, namely the metabolic syndrome, are well established. Syndrome risk factors/conditions are abdominal obesity, insulin resistance/glucose intolerance, hypertension, and dyslipidemia and are associated with significantly increased risk of cardiovascular disease and diabetes[4]. Several definitions of the syndrome have been put forward[5], but the most commonly cited criteria are those of the Adult Treatment Panel III (ATP III), the third report of an expert committee of the National Cholesterol Education Program (NCEP). ATP III criteria require at least three of the following conditions for diagnosis of the Metabolic Syndrome: waist circumference >102 cm (men) >88 cm (women); fasting glucose ≥110 mg/dL; blood pressure ≥130/85 mmHg; triglycerides ≥150 mg/dL; and HDL cholesterol <40 mg/dL (men) <50 mg/dL (women). Not surprisingly, this obesity-linked syndrome has also reached epidemic proportions globally, with prevalence estimates approaching 1 billion worldwide[5].

Several etiological factors have been proposed to explain the recent global increase in obesity and obesity-related health problems. 'Thrifty' genetic factors have been emphasized, especially in ethnic groups with the highest obesity prevalence[6]. Attention has also focused on increasingly common 'modern' lifestyles risk factors, including minimal physical activity and high energy, high fat, low fiber (i.e., »western«) diets[7]. In addition, experimental animal and epidemiological research focusing on the developmental origins of health and disease (DOHaD)

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has revealed processes beginning in the periconceptual and embryonic period[8] and extending throughout postnatal growth[9,10] that are increasingly recognized as critical in the growth of obesity and obesity-related disorders. The effects of maternal nutrition during pregnancy and lactation on the development of obesity and its related diseases are well established, especially in animal models[10–12].

Analysis of several human populations with exceptionally high prevalence of obesity and type 2 diabetes, such as the Pima Indians of southern Arizona, reveal common periods of severe socio-economic disruption and nutritional deprivation in the recent past[13]. These same high-risk populations have also undergone very recent and rapid transformations in lifestyle and dietary patterns. Such patterns are consistent with a developmental model of childhood and adult obesity and its health-related sequelae, although the relative importance of developmental factors in the epidemic of obesity – relative to other etiological factors – remains to be precisely determined. There remains little doubt, however, that developmental factors play a significant role[14,15]. The extent to which local explanations of obesity-related health problems coincide with DOHaD research findings may have important implications for local, community-based prevention efforts[16], should ongoing research support the implementation of such population-based public health initiatives in the future.

The First Developmental Pathway to Obesity: Maternal 'Famine'

Observational studies in human populations and experimental animal studies reveal developmental processes which link undernutrition during gestational and perinatal life with a propensity to increased adiposity in adulthood.

Epidemiological Studies

Strong links between poor nutrition during pregnancy and/or small size at birth, and the subsequent risk of obesity and its related metabolic disorders in adulthood among humans are well established[17]. In one of the most widely cited studies, Ravelli and coworkers showed that early fetal undernutrition, as a consequence of the 'Dutch Hunger Winter' of WWII, was associated with offspring obesity later in life[18]. Especially if occurring late in fetal life, undernutrition during gestation can result in full term neonates that are of low birth weight (<2.5 kg). These newborns are usually referred to as small for gestational age (SGA). In addition to weight, small size at birth can also be measured in other ways, including birth length, ponderal index (weight/length^3), body mass index (BMI) and head circumference. While newborns can be SGA due to a number of conditions, including genetic abnormalities, exposure to toxins, and parasitic infections, among others, it is most often the result of one of three factors: maternal undernutrition during pregnancy, maternal constraint, and/or maternal smoking during pregnancy[19]. Maternal undernutrition can be caused by insufficient total energy intake (global undernutrition), macronutrient (e.g., protein) or micronutrient (e.g., folate) deficiencies[19]. Alternatively, maternal constraint refers to suppressed fetal growth as a result of maternal size, parity and possibly age[15]. Maternal smoking retards fetal growth via a number of physiological mechanisms as well, and its association with SGA infants is also well established[20].

While epidemiological studies have shown that being small at birth does predict later obesity[21], small size at birth may not be sufficient to predispose small infants to obesity or the more metabolically dangerous form of fat deposition – abdominal obesity – in adulthood. Epidemiological research among a number of populations has shown that it is the children born small at birth that subsequently go through rapid periods of postnatal, or »catch-up« growth (after infancy), who are most susceptible to abdominal obesity and the metabolic syndrome later in life[22]. Perhaps most importantly, it is the *timing* of catch-up growth, during the so-called »adiposity rebound« that has emerged as the most critical factor. Normally, adiposity increases in infants through the first year of life, and then begins a five to six year decline. The timing of when fat stores once again begin to rise (the »adiposity rebound« period) at around six years of age, is the best single predictor of adult obesity and diabetes. Children who begin the adiposity rebound period »early« (< 5.5 years of age), show a significantly higher level of adiposity than children who rebound »late« (> 7 years of age)[9,23].

Several epidemiological studies also suggest that size at birth is a better predictor of the distribution of body fat than gross measures of overall fatness (e.g., BMI). Some of these studies report that birth weight correlates more strongly with adult height, weight and muscle mass than adiposity per se[24]. Specifically, low birth weight is strongly associated with abdominal or 'truncal' fat deposition. Young adult Mexicans and non-Hispanic Americans with low birth weights, for example, were found to have greater abdominal fat deposits than their higher birth weight counterparts, as measured by high subscapular to triceps skinfold ratios[25]. A study of 7 to 12-year-old American children reported similar findings[26], and in Asia, the Pune Nutritional Study has shown that babies born to short and thin women in rural India were small at birth (mean full-term birth weight = 2.7 kg) and, compared to white babies born in the UK, had less muscle mass, and relatively more truncal fat[27], a body composition pattern that appears to persist into adulthood[28,29]. These effects also appear to be exacerbated by weight gain during adipose rebound. In an English study, teenage girls who were smallest at birth, but with the greatest adiposity in their middle teen years, had the highest levels of truncal fat[30].

Animal Models

Experimental animal studies have contributed greatly to DOHaD research. Unlike human studies, animal research allows for carefully controlled genetic and envi-

ronmental influences, diet manipulation and unfettered histological assessment, in addition to short gestational and maturation cycles in many species.

Like the bulk of epidemiological research on the developmental factors involved in obesity, animal studies have found that a variety of maternal dietary restrictions during gestation lead to reduced birth size, and a subsequent increase in adiposity and metabolic disorders in mature offspring. These studies have been carried out among a large variety of animal species, including mice, rats, guinea pigs, rabbits, pigs and sheep[10,31,32].

At least in rats, *ad libitum* protein- and iron-restricted maternal diets during pregnancy and the suckling period do not generally lead to increased body weights and adiposity in low birth weight offspring when animals are weaned onto a control diet[33,34]. Total caloric restriction of pre- and perinatal maternal diets, however, is associated with hyperphagia, decreased locomotor activity, and increased adiposity in adult male and female offspring after animals are weaned onto control diets[35–37]. In addition, studies with sheep, which model the human propensity for abdominal fat deposition especially well, also show increased adiposity in adulthood when mothers are exposed to nutrient-restricted diets during pregnancy[38–40].

»Catch-up« growth is being increasingly modeled in animal research also[41]. In an important recent study with mice[42], Jimenez-Chillaron and collegues reported that animals that were low birth weight (LBW) due to maternal undernutrition during pregnancy *and* exhibited early postnatal catch-up growth (in the first week of life), developed obesity and glucose intolerance by 6 months of age. Interestingly, maternally-malnourished, LBW animals that were placed on calorically-restricted control diets postweaning did not exhibit early catch-up growth, and did not become glucose intolerant or obese in adulthood. Moreover, control animals that were weaned onto the calorically-restricted diet postweaning, and, as a result, showed blunted postnatal growth compared to control animals weaned onto control diets, were leaner and showed superior glucose tolerance than control animals fed a control diet postweaning.

While such developmentally programmed effects are generally thought to become 'fixed' during early development and thus persist throughout adulthood, some plasticity in the early postnatal period has been observed[43]. Vickers and colleagues have shown that if offspring of female rats that were undernourished during pregnancy are treated neonatally with leptin – a hormone critical to the regulation of body weight and appetite – their body weights, fat mass, insulin and glucose levels remain normal in adulthood, in contrast to untreated animals.

The Second Developmental Pathway to Obesity: Maternal 'Feast'

Human-observational and experimental animal studies have shown that in addition to developmentally programmed adjustments to nutritional deficits during prenatal and perinatal life, nutritional surplus during the same critical periods can also lead to developmentally programmed predispositions to increased adipose deposition in later years.

Epidemiological Studies

Clinical and epidemiological studies have demonstrated that both pre-pregnancy obesity and maternal obesity during pregnancy are associated with relatively fat and large (>4.0 kg) neonates[44–47]. These large for gestational age (LGA) children are, in turn, significantly more susceptible to obesity and metabolic syndrome in later years[48]. In terms of fat deposition, whether this is due to changes in the fat cell itself, appetite regulation, hormonal signaling, or some combination of these factors, remains to be determined[40]. What is known from a large number of epidemiological and clinical studies is that exposure to the diabetic intrauterine environment substantially increases the risk of obesity and diabetes among exposed offspring in adulthood[49–51].

Other studies have shown that rapid weight gain *after* birth, in the neonatal period, is associated with obesity in later life[52,53]. Plagemann and colleagues report that neonates breast-fed by their diabetic mothers, as opposed to being fed »banked« breast milk from non-diabetic mothers, were more likely to become overweight later in childhood. These authors suggest that higher concentrations of glucose and/or insulin in the breast milk of diabetic mothers may be responsible for the increased risk[54]. A recent study of over 15,000 children, conducted by Mayer-Davis and colleagues[55] found that breast-feeding was protective against childhood obesity, regardless of maternal diabetes status. Thus, while the obesity-inducing or protective effects of human breast-milk of diabetic mothers remains to be clarified, there is accumulating evidence from human and animal studies that, as a general principle, maternal overnutrition during prenatal and perinatal life is likely to lead to the permanent programming of the neuro-endocrine system that predisposes to obesity and its related health risks[11,12]. Insulin and leptin, key hormones in the regulatory control of food intake, body weight and metabolism, are two of the most commonly identified teratogens in this hypothesized developmental pathway[12].

Animal Models

In a host of experimental studies with rodents, maternal overfeeding during pregnancy and lactation results in a constellation of phenotypic traits in the offspring that is very similar to the metabolic syndrome in humans, and includes abnormal glucose tolerance, increased blood pressure, and dyslipidemia, in addition to and increased adiposity[10,31,32]. Interestingly, offspring of dams fed high fat diets (24–40% of energy) during pregnancy or pregnancy and lactation, but fed control diets after weaning, have lower basal metabolic rates, and higher body weights and fat mass than controls animals[56–58], while offspring of dams fed high fat diets during pregnancy/lactation and weaned onto similar high fat diets, became frankly obese in adulthood[57].

Consistent with findings from clinical and epidemiological studies with humans, gestational diabetes (chemically-induced) in experimental female animals results in offspring that are glucose intolerant, hyperphagic, and overweight in adulthood[59,60]. In animal research focusing on early postnatal life, rats that are overfed during suckling become hyperphagic, hyperinsulinemic, glucose intolerant, hypertensive, and overweight when they mature[12].

The developmentally-programmed, metabolic traits described above have also been shown to be transmissible to subsequent generations. Both chemically- and nutritionally-induced glucose intolerance models have shown that altered insulin-glucose metabolism is transmissible to second and third generation experimental animals[33,53,59,61]. In the nutritionally-induced animal models, these studies are clear evidence that developmentally programmed metabolic traits can be transmitted across multiple generations through a combination of »famine« (i.e., maternal undernutrition) and »feast« (i.e., gestational diabetes) pathways in a single matrilineal line[33,61,62]. Whether or not these metabolic developmental effects might be accompanied by a predisposition to greater adiposity during adulthood in second (F2) and third (F3) generation offspring, however, awaits further research.

Anthropological Perspectives on the Development of Obesity and Related Health Disorders

Evolutionary Implications

While the relationship between developmental environments of fetal and perinatal life and later susceptibility to disease in adulthood has usually been interpreted in the context of human pathology and epidemiology, there is a growing interest in the possible evolutionary significance of these predispositions. Attempts to explain this relationship in evolutionary terms include the »Predictive Adaptive Response« (PAR) hypothesis[63] and the Phenotypic Inertia hypothesis[64]. In the PAR model, prenatal and early postnatal nutritional environments are hypothesized to anticipate nutrient availability in later life, and consequently, phenotypically accommodate to these likely future environments by programming metabolic function and capacity accordingly – thereby optimizing adaptation to the 'predicted' postnatal environment. Alternatively, the »Phenotypic Inertia« hypothesis suggests that the flow of nutrients to the developing fetus represents an »integrated signal« reflecting matrilineal nutrition over multiple generations, and as such, acts as a buffer against the »noise« of short-term seasonal or stochastic fluctuations within longer-term ecological trends.

Although a large body of animal model research exists on the effects early developmental environments have on adult health, and several novel (rich prenatal/rich postnatal diet) one-generation animal studies provide some support for the PAR hypothesis[41,58,65], very few studies have been designed to assess the heritability of these effects over multiple generations, their impact on survival or reproductive fitness – and thus their potential adaptive significance. What few studies have been done suggest a trend toward 'normalization' of developmentally-programmed traits in successive generations[61,66]. As a result, the potential evolutionary significance of developmentally-programmed intergenerational effects remains highly speculative at this time, and awaits further empirical tests of these and other, alternative hypotheses.

A Reconsideration of Contemporary 'Ethnic/Racial' Health Disparities

DOHaD research has provided an opportunity to reassess long-standing assumptions about presumed ethnic/racial genetic predispositions to obesity and related metabolic disorders[13,28,67]. Yajnik argues that the obesity epidemic in India may be largely due to »compromised« nutrition during pregnancy, and suggests that poor prenatal diets are most likely to be found in India and other developing countries. He further proposes that the developmental processes that underlie the predisposition to abdominal obesity may be rooted in the propensity to spare brain growth at the cost of other tissues during intrauterine life if maternal nutrition is limited.

The obesity/type 2 diabetes epidemic among Native Americans has also been interpreted in light of DOHaD research. Investigators have noted that the Native American populations with highest reported prevalence of obesity and type 2 diabetes all share common recent histories of severe cultural and economic disruptions and prolonged nutritional stress, followed by rapid transitions to western diets and sedentary lifestyles – conditions which are most conducive to the 'feast' and 'famine' developmental pathways outlined above (see Table 1). Given the socio-historical conditions under which the developmental pathways to obesity/diabetes may have become manifest in these Native populations, these authors have urged a reconsideration of the 'thrifty-genotype' etiology of these disorders among the highest prevalence Native American groups, and have suggested diabetes among these populations constitutes a »political disease«[13]. Comparable extended periods of social and economic disruption and nutritional stress are also evident in other Indigenous and migrant populations with high prevalence of obesity/diabetes outside of Native North America (see Table 2).

Implications for Applied Medical Anthropology and Public Health

The potential implications of the developmental origins of obesity and its related health disorders for public health interventions are profound. In a best case scenario, some researchers have suggested that by helping high risk mothers carefully control their blood sugar during pregnancy, the familial chain of diabetes might be broken altogether[95]. In a similarly prospective vein, Benyshek[16] argues that among Native American populations with some of the highest risk for obesity and type 2 diabetes in the world, primary prevention programs that

TABLE 1[13]
SELECTED NATIVE AMERICAN POPULATIONS WITH TYPE 2 DIABETES PREVALENCE OVER 15%

Population	Published Type 2 Diabetes Prevalence	Conditions/Periods of Deprivation
Pima	Male – 49.9% Female – 51.1% [68]	1870–1960s drought; loss of irrigation water; reservation poverty[69–71]
Oji-Cree	M/F – ~ 40.0% [72]	1820–1950s over-trapping/hunting; collapse of traditional subsistence econ.; native settlement poverty[73,74]
Havasupai	M – 38.0% F – 55.0% [75]	1880–1960s concentration; collapse of traditional subsistence econ.; reservation poverty[76,77]
Cocopah	M/F – 33.0% [68]	1850–1960s concentration; collapse of traditional subsistence econ.; reservation poverty[78,79]
Seneca	M/F – 33.5%[80]	1800–1960s concentration; loss of traditional lands/resources; reservation poverty[81,82]

TABLE 2
SELECTED INDIGENOUS AND MIGRANT POPULATIONS WITH TYPE 2 DIABETES PREVALENCE OVER 15%

Other Indigenous Populations	Published Type 2 Diabetes Prevalence	Conditions/Periods of Deprivation
Nauru	Male – 40.6% Female – 40.2%[83]	1890–1960s military occupation; forced labor; poverty[84–86]
Aboriginal Australian	M – 24.0% F – 28.9%[87]	1800–1970s forced relocation; concentration; reserve poverty[88,89]
Migrant Populations		
Fiji Indians	M – 23.6% F – 20.3%[90]	1880–1940s indentured labor; manual labor; enclave poverty[91]
Singapore Indians	M – 22.7% F – 10.4%[92]	1850–1940s indentured labor; manual labor; enclave poverty[93]
Singapore Malayans	M – 16.1% F – 13.3%[92]	1840–1970s manual labor migration; enclave poverty[94]

would focus on improved prenatal care and nutrition would be likely to enjoy significantly increased community support and participation due to the fact that developmental etiological models of obesity and diabetes reinforce and validate commonly held local ideas about the root causes of these epidemics.

Other researchers, however, sound a more cautious tone. These authors warn that a great deal more must be learned from clinical, epidemiological and experimental animal studies before effective and ethical developmentally-targeted interventions – especially those focusing on prenatal care – can be implemented[96]. With respect to nutritional interventions aimed at reducing low birth weight, the only immediate nutritional intervention that has been shown to be consistently effective is energy/protein supplementation among undernourished mothers. At present, evidence from observational and intervention studies that assess the effectiveness of interventions aimed at preventing low birth weight via supplementation of specific micronutrients (e.g., iron, folate) are either lacking or inconclusive[19]. Other reasons given for proceeding with caution include the difficulties involved in whole-population (versus 'targeted') public health approaches, and the challenges of safely and effectively altering childhood growth patterns at different ages. In addition, ethical concerns regarding prenatal interventions have been raised, including the possibility that improving fetal growth (in order to improve health outcomes for the child), may lead to increased obstetric complications and maternal mortality[97], in addition to the risks associated with shifting blame from disease-causing genes to 'irresponsible mothers' who put their babies at risk by mismanaging their pregnancies[13,96]. Finally, even if such programs could be shown to be safe and effective, and the ethical issues surrounding them resolved, how such programs would be financed is of great concern. This is par-

ticularly true in developing countries and among economically disadvantaged groups in developed ones, where, not only is risk greatest, but public health resources are the scarcest[14].

Current research has firmly established that events in prenatal and perinatal life are crucial factors in the development of obesity and obesity-related disorders in adulthood. Whether or not developmentally-oriented public health initiatives aimed at preventing obesity and its sequelae should and can be successfully implemented remains a matter of debate. Anthropology remains well positioned to contribute to these areas of research and debate because of its potential to provide unique insights into the evolutionary context of human evolution, growth and development, and its ability to provide local ethnographic context and cross-cultural socio-historic perspectives to bear on DOHaD issues.

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RAZVOJNO PORIJEKLO DEBLJINE I POVEZANIH ZDRAVSTVENIH POREMEĆAJA – PRENATALNI I PERINATALNI FAKTORI

S A Ž E T A K

Debljina i metabolički sindrom u posljednje vrijeme prerasli su u globalnu zdravstvenu krizu. Prevalencija debljine u djetinjstvu i odrasloj dobi u ekonomski razvijenim i zemljama u razvoju više je nego udvostručena u zadnjem desetljeću. Iako su genetski faktori, povećanje sjedilačkog načina života i prekomjerna prehrana bili navođeni kao važni uzročnici krize debljine, noviji epidemiološki i eksperimentalni dokazi sugeriraju da razvojni faktori – pogotovo oni koji se zbivaju tijekom intrauterinog razvitka i tijekom rane postnatalne faze života, igraju značajnu ulogu u ovoj pandemiji. Istraživanja razvojnog porijekla debljine i bolesti čvrsto su utvrdila da prenatalne i perinatalne perturbacije, koje mogu biti predispozicija za debljinu u odrasloj dobi, mogu biti rezultat brojnih faktora, uključujući suvišak i nedostatak hrane, te se pojavljuje sve više dokaza da se ova fiziološka svojstva mogu epigenetski prenositi na sljedeće generacije. Antropološka perspektiva vezana uz razvojno porijeklo debljine i povezanih zdravstvenih poremećaja, ne samo da može rasvijetliti nejednakosti zdravlja današnjih etničkih grupacija, već može i javno zdravstvenim projektima na nivou zajednice pružiti jedinstveni uvid u važnost razvojnog porijekla bolesti.